

Sub B'

What is claimed is:

1. A method for treating hyperlipidemia in a
5 mammal, said method comprises a step of administering
to said mammal an effective amount of an RAR
antagonist or an RAR inverse agonist.

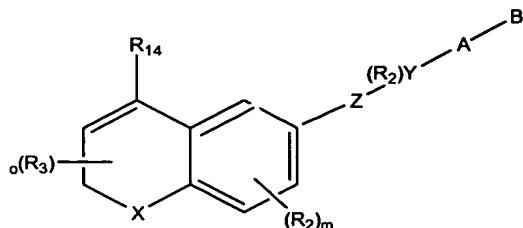
10 2. A method of claim 1 wherein said RAR is
selected from the group consisting of RAR α , RAR β , and
RAR γ .

15 3. A method of claim 1 wherein said RAR
antagonist or an RAR inverse agonist is effective to
lower the level of circulating lipid in a mammal,
including a human being.

20 4. A method of claim 1 wherein said RAR
antagonist or an RAR inverse agonist is effective to
lower the level of circulating triglyceride in a
mammal, including a human being.

Sub A 5. A method of claim 1 wherein the step of
25 administering said RAR antagonist or an RAR inverse
agonist further prevents myocardial infarction.

30 6. A method of claim 1 wherein said RAR
antagonist or RAR inverse agonist has the chemical
structure:



Sub C' Cont 30 wherein X is S, O, NR' where R' is H or alkyl of 1
to 6 carbons, or

X is [C(R₁)₂]_n where R₁ is independently H or alkyl

of 1 to 6 carbons, and n is an integer between, and including, 0 and 2, and;

R₂ is independently hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro substituted alkyl of

5 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

R₃ is independently hydrogen, lower alkyl of 1 to 6 carbons or F, and;

m is an integer having the value of 0 - 3, and;

10 o is an integer having the value of 0 - 3, and;

Z is -C≡C-,

-N=N-,

-N=CR₁-,

-CR₁=N,

15 -(CR₁=CR₁)_{n'}- where n' is an integer having the value 0 - 5,

-CO-NR₁-,

-CS-NR₁-,

-NR₁-CO,

20 -NR₁-CS,

-COO-,

-OCO-;

-CSO-;

-OCS-;

25 Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thiienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one 30 or two R₂ groups, or

when Z is -(CR₁=CR₁)_{n'}- and n' is 3, 4 or 5 then Y represents a direct valence bond between said (CR₂=CR₂)_{n'} group and B;

35 A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

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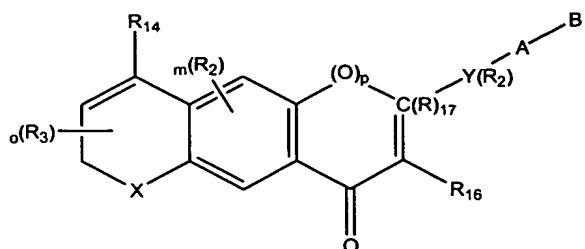
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B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, and

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25

R₁₄ is (R₁₅)_r-phenyl, (R₁₅)_r-naphthyl, or (R₁₅)_r-heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5, and R₁₅ is independently H, F, Cl, Br, I, NO₂, N(R₈)₂, N(R₈)COR₈, NR₈CON(R₈)₂, OH, OCOR₈, OR₈, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons.

7. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



wherein X is S, O, NR' where R' is H or alkyl of 1

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to 6 carbons, or

X is $[C(R_1)_2]_n$ where R_1 is independently H or alkyl of 1 to 6 carbons, and n is an integer between, and including, 0 and 2, and;

5 R₂ is independently hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF₃, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

10 R₃ is independently hydrogen, lower alkyl of 1 to 6 carbons or F, and;

m is an integer having the value of 0, 1, 2, or 3, and;

o is an integer having the value of 0, 1, 2, or 3, and;

15 Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one 20 or two R₂ groups, and;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or tri-lower alkylsilyl, where R₇ is an alkyl, 30 cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently 35 are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, and;

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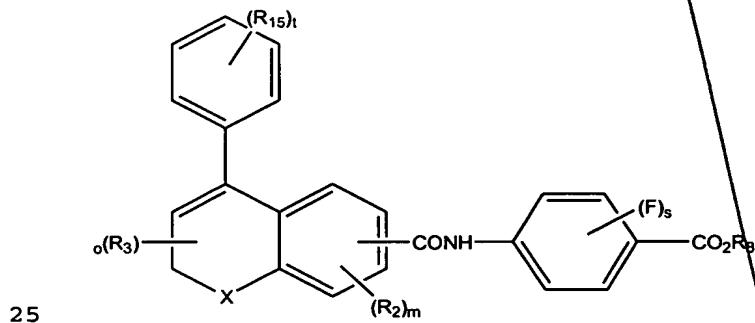
5 R_{14} is $(R_{15})_r$ -phenyl, $(R_{15})_r$ -naphthyl, or $(R_{15})_r$ -heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0, 1, 2, 3, 4 or 5, and;

10 R_{15} is independently H, F, Cl, Br, I, NO_2 , $N(R_8)_2$, $N(R_8)COR_8$, $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8 , CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons, and;

15 R_{16} is H, lower alkyl of 1 to 6 carbons, and;
 R_{17} is H, lower alkyl of 1 to 6 carbons, OH or $OCOR_{11}$, and;

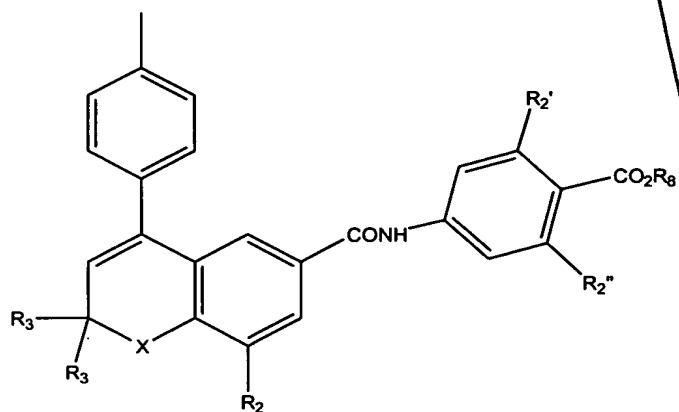
20 p is zero or 1, with the proviso that when p is 1 then there is no R_{17} substituent group, and m is an integer between, and including, 0 and 2.

25 8. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



where X is $C(R_1)_2$, or O, and;
 R_1 is H or alkyl of 1 to 6 carbons, and;
 R_2 is independently lower alkyl of 1 to 6 carbons, F,
30 Cl, Br, I, CF_3 , fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

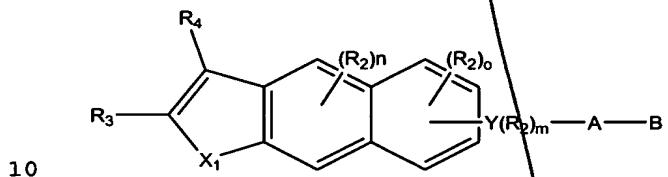
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- m is an integer having the value of 0-3, and;
R₃ is independently lower alkyl of 1 to 6 carbons or F,
and;
- o is an integer having the value of 0-3, and;
- 5 s is an integer having the value of 1-3, and;
R₈ is an alkyl group of 1 to 10 carbons or
trimethylsilylalkyl where the alkyl group has 1 to 10
carbons, or a cycloalkyl group of 5 to 10 carbons, or
R₈ is phenyl or lower alkylphenyl, and;
- 10 R₁₅ is independently H, F, Cl, Br, I, NO₂, N(R₈)₂, COR₈,
NR₈CON(R₈)₂, OCOR₈, OR₈, CN, an alkyl group having 1 to
10 carbons, fluoro substituted alkyl group having 1 to
10 carbons, an alkenyl group having 1 to 10 carbons
and 1 to 3 double bonds, an alkynyl group having 1 to
10 carbons and 1 to 3 triple bonds, or a trialkylsilyl
or trialkylsilyloxy group where the alkyl groups
independently have 1 to 6 carbons, and;
- 15 t is an integer having the values of 0, 1, 2, 3, 4, or
5, and;
- 20 the CONH group is in the 6 or 7 position of the benzopyran, and in the 2 or 3 position of the dihydronaphthaline ring, or a pharmaceutically
acceptable salt of said compound.
- 25 9. A method of claim 1 wherein said RAR
antagonist or RAR inverse agonist has the chemical
structure:



30 where X is C(CH₃)₂ or O, and;

~~R₂ is H or Br, and;
R₂, and R₂, independently are H or F, and;
R₃ is H or CH₃, and;
R₈ is H, lower alkyl of 1 to 6 carbons, or a
pharmaceutically acceptable salt of said compound.~~

10. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:

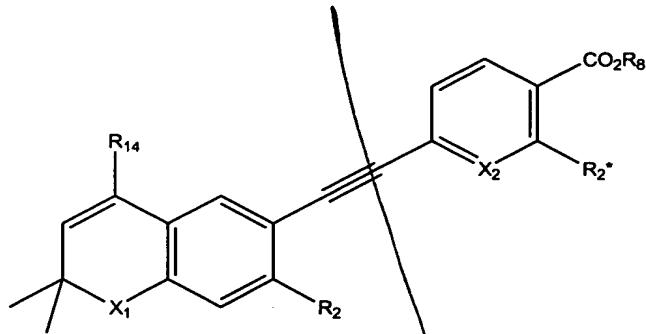


wherein X_1 is: $-C(R_1)_2-$, $-C(R_1)_2-C(R_1)_2-$, $-S-$, $-O-$, $-NR_1-$, $-C(R_1)_2-O-$, $-C(R_1)_2-S-$, or $C(R_1)_2-NR_1-$; and
15 R_1 is independently H or alkyl of 1 to 6 carbons; and
 R_2 is optional and is independently defined as lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , fluoro substituted alkyl of 1 to 6 carbons, OH SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons; and
20 m is an integer between, and including, 0 and 4; and
 n is an integer between, and including, 0 and 2; and
 o is an integer between, and including, 0 and 3; and
 R_3 is H, lower alkyl of 1 to 6 carbons, F, Cl, Br or I; and
25 R_4 is $(R_5)_p$ -phenyl, $(R_5)_p$ -naphthyl, $(R_5)_p$ -heteroaryl where the heteroaryl group is five-membered or 6-membered and has 1 to 3 heteroatoms selected from the group consisting of O, S, and N; and
 p is an integer between, and including, 0 and 5; and
30 R_5 is optional and is defined as independently F, Cl, Br, I, NO_2 , $N(R_8)_2$, $N(R_8)COR_8$, $N(R_8)CON(R_8)_2$, OH, $OCOR_8$, OR_8 , CN, COOH, $COOR_8$, an alkyl group having from 1 to 10 carbons, an alkenyl group having from 1 to 10 carbons and 1 to three double bonds, alkynyl group having from 1 to 10 carbons and 1 to 3 triple bonds, or a (trialkyl)silyl or (trialkyl)silyloxy group where

the alkyl groups independently have from 1 to 6 carbons; and

- Y is a phenyl or naphthyl group, or a heteroaryl selected from the group consisting of pyridyl, 5 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R₂ groups, or Y is - (CR₃=CR₃)_r-; and
- 10 r is an integer between, and including, 1 and 3; and A is (CH₂)_q where q is an integer from 0-5, lower branched chain alkyl having from 3 to 6 carbons, cycloalkyl having from 3 to 6 carbons, alkenyl having from 2 to 6 carbons and 1 or 2 double bonds, alkenyl 15 having from 2 to 6 carbons and 1 or 2 triple bonds, with the proviso that when Y is -(CR₃=CR₃)_r- then A is (CH₂)_q and q is 0; and B is H, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, 20 CH(OR₁₂)₂, CHOR₁₃O, -COR₇, CR₇(OR₁₂)₂, CR₇OR₁₃O, or Si(C₁-alkyl)₃, wherein R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl, where the alkyl groups has 1 to 10 carbons, or a cycloalkyl 25 group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are H, a lower alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower 30 alkyl, and R₁₃ is a divalent alkyl radical of 2-5 carbons.

11. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



wherein X_1 is S or O;

X_2 is CH or N;

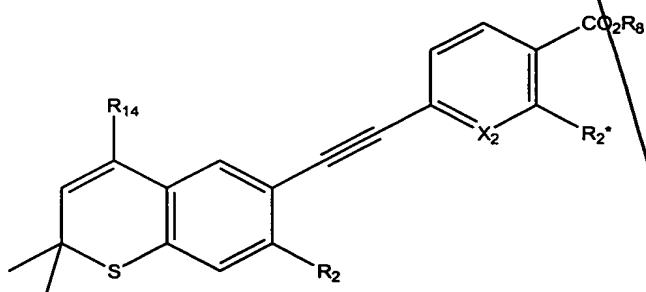
5 R_2 is H, F, CF_3 , or alkoxy of 1 to 6 carbons;

R_2^* is H, F, or CF_3 ;

R_8 is H, or lower alkyl of 1 to 6 carbons;

10 R_{14} is unsubstituted phenyl, thienyl or pyridyl, or phenyl, thienyl or pyridyl substituted with one to three R_{15} groups, where R_{15} is lower alkyl of 1 to 6 carbons, chlorine, CF_3 , or alkoxy of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

12. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



20 wherein X_2 is CH or N, and;

R_2 is H, F, or OCH_3 , and;

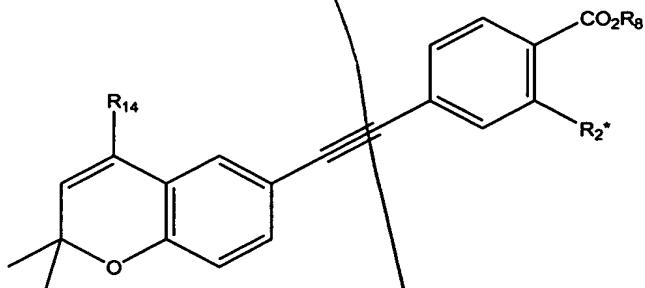
R_2^* is H or F, and;

R_8 is H, or lower alkyl of 1 to 6 carbons, and;

25 R_{14} is selected from the group consisting of phenyl, 4-(lower-alkyl)phenyl, 5-(lower alkyl)-2-thienyl, and 6-(lower alkyl)-3-pyridyl where lower alkyl has 1 to 6 carbons, or a pharmaceutically acceptable salt of said

compound.

13. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:

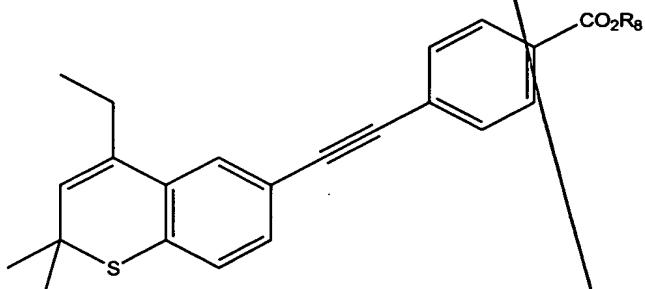


where R_2^* is H or F;

R_8 is H, or lower alkyl of 1 to 6 carbons, and

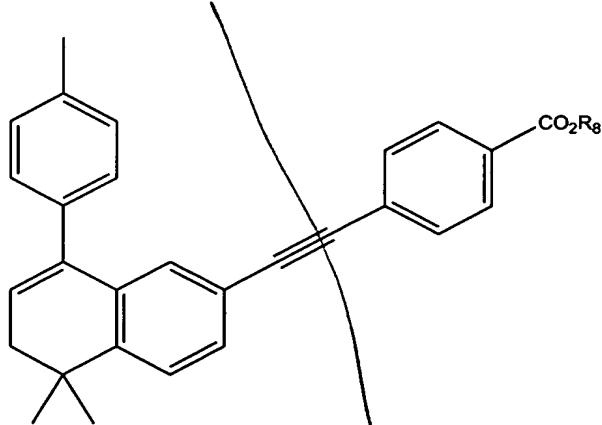
R_{14} is selected from the group consisting of phenyl, and 4-(lower-alkyl)phenyl, where lower alkyl has 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

14. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



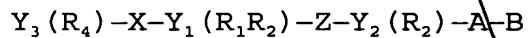
20 where R_8 is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

15. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



where R_8 is H, lower alkyl of 1 to 6 carbons, or a pharmaceutically acceptable salt of said compound.

5 16. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



10 Where Y_1 is phenyl, naphthyl, or heteroaryl selected from the group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazonyl, ozazolyl, imidazolyl, and pyrrazolyl, said phenyl, naphthyl, and heteroaryl groups being substituted with an R_1 group, and further substituted or unsubstituted with one or two R_2 groups;

15 R_1 is C_{1-10} alkyl, 1-ademantyl, 2-tetrahydropyranoxy, trialkylsilyloxy where alkyl has up to 6 carbons, OH, alkoxy where the alkyl group has up to 10 carbons, alkylthio where the alkyl group has up to 10 carbons, or OCH_2OC_{1-6} alkyl;

20 R_2 is lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3 , CF_2CF_3 , OH, OR_3 , NO_2 , $N(R_3)_2$, CN, N_3 , COR_3 , $NHCOR_3$, COOH, or $COOR_3$;

25 X is $(C(R_3)_2$, S, SO, SO_2 , O or NR_3 ;

Z is $-C\equiv C-$,

$-N=N-$,

$-N(O)=N-$,

$-N=N(O)-$,

$-N=CR_3-$,

30 $-CR_3=N$,

- $(CR_3=CR_3)_n$ - where n is an integer having the value 0 - 5,

5 - CO-NR₃ -,

 - CS-NR₃ -,

 - NR₃-CO,

 - NR₃-CS,

 - COO-,

 - OCO-;

 - CSO-;

10 - OCS-; or

 - CO-CR₃=R₃-O,

R₃ is independently H or lower alkyl of 1 to 6 carbons;

15 Y₂ is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one or two R₂ groups, or

20 when Z is - $(CR_3=CR_3)_n$ - and n is 3, 4 or 5 then Y₂ represents a direct valence bond between said - $(CR_3=CR_3)_n$ group and B;

25 Y₃ is phenyl, naphthyl, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one to three R₄ groups, where R₄ is alkyl of 1 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 triple bonds, F, Cl, Br, I, NO₂, CN, NR₃, N₃, COOH, COOC₁₋₆ alkyl, OH, SH, OC₁₋₆ alkyl, and SC₁₋₆ alkyl;

30 A is (CH₂)_q where q is from 0-5, lower branched alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl, having 2-6 carbons and 1-2 double bonds, alkynyl having 2-6 carbons and 1 to 2 triple bonds, and

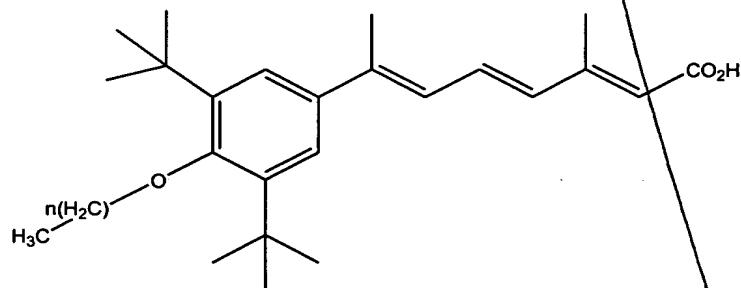
35 B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁,

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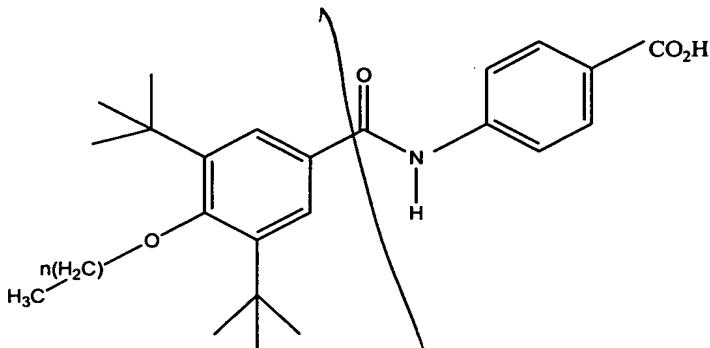
CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CHOR₁₃O, -COR₁₄, CR₁₅(OR₁₂)₂, CR₁₆OR₁₃O, or Si(C₁₋₆ alkyl)₃, where R₁ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or 5 trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or 10 phenyl or lower alkylphenyl, R₁₁ is lower alkyl, phenyl or lower alkylphenyl, R₁₂ is lower alkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons, or a pharmaceutically acceptable salt of said compound.

15 17. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



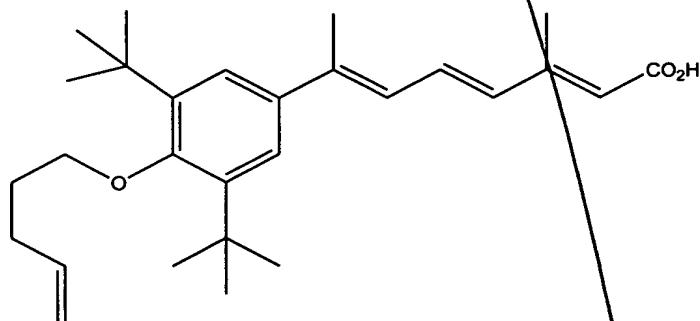
20 where n is an integer from 1 to 10.

18. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical 25 structure:

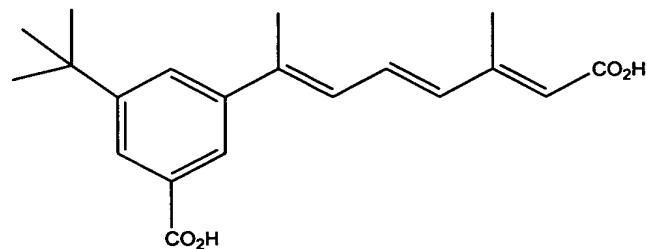


where n is an integer from 1 to 10.

- 5 19. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:

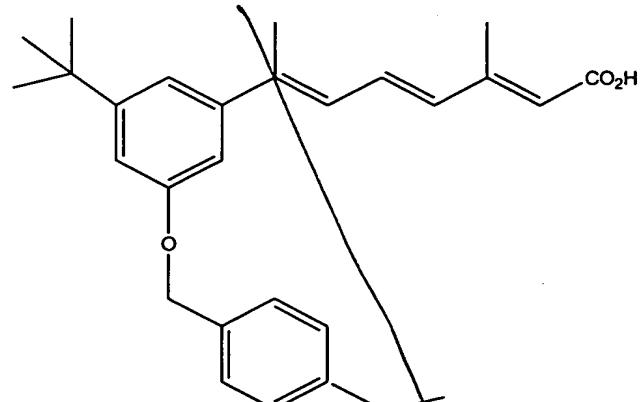


- 10 20. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:



- 15 21. A method of claim 1 wherein said RAR antagonist or RAR inverse agonist has the chemical structure:

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22. A method of claim 1 wherein the RAR antagonist or an RAR inverse agonist is administered orally.

23. A method of claim 1 wherein the RAR antagonist or an RAR inverse agonist is administered topically.

24. A method of claim 1 wherein the RAR antagonist or an RAR inverse agonist is administered systemically.

25. A method for treating hyperlipidemia in a mammal, said method comprises a step of administering to said mammal an effective amount of 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid (AGN 194310).

26. A method of claim 24 wherein the step of administering 4-[[4-(4-ethylphenyl)-2,2-dimethyl-(2H)-thiochromen-6-yl]-ethynyl]-benzoic acid lowers the level of circulating triglycerides (AGN 194310).